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Analysis of West Virginia Medicaid Claims Data for the Prevalence of Medical Conditions and Use of Drugs Likely to Cause QT Prolongation in Patients with Schizophrenia

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ABSTRACT

Background: An important concern with antipsychotic drugs used for the treatment of schizophrenia is the prolongation of the QT interval on the electrocardiogram. Concomitant use of other QT-prolonging drugs and the presence of certain medical conditions may lead to excessive QT prolongation and subsequent cardiac arrhythmias.

Objective: The aim of this study was to assess the utilization of QT-prolonging drugs and the prevalence of medical conditions causing QT prolongation in a large population of patients with schizophrenia in practice settings.

Methods: The study was conducted using West Virginia Medicaid claims data for patients aged 18 to 64 years with ≥1 medical claim for schizophrenia between January 1, 1997, and December 31, 1999. A comprehensive list of drugs and medical conditions causing QT prolongation was obtained from the literature. The drugs were identified in the prescription claims data using their specific National Drug Classification codes. Codes from the *International Classification of Diseases, Ninth Revision, Clinical Modification*, were used to identify the medical conditions as described in the medical claims files. Descriptive statistics on utilization of drugs and prevalence of medical conditions were reported and demographic differences were examined.

Results: The final sample consisted of 1699 patients with schizophrenia. The mean (SD) age was 40.8 (11.35) years (range, 18–63 years); 55% of the patients were women. A total of 76.9% of patients utilized ≥1 nonantipsychotic QT-prolonging drug in a year, with a mean (SD) of 2.1 (1.3) such drugs used per

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patient per year. A total of 15.9% of patients with schizophrenia had ≥1 medical condition associated with QT prolongation. Patients with ≥1 such medical condition had a mean (SD) of 1.2 (0.57) conditions potentially causing QT prolongation. The number of nonantipsychotic QT-prolonging prescriptions filled and the prevalence of medical conditions leading to QT prolongation were found to be significantly higher for women (both $P < 0.001$) and patients aged 34 to 64 years (both $P < 0.001$).

Conclusions: In this study, a high utilization of QT-prolonging drugs and the prevalence of medical conditions causing QT prolongation were found. These results merit assessment of predisposing risk factors, such as concurrent use of other QT-prolonging drugs and the presence of cardiovascular and other conditions associated with QT prolongation, before prescribing antipsychotics, especially in women and older patients with schizophrenia. (*Curr Ther Res Clin Exp.* 2003;64:538–550)

Key words: Medicaid, schizophrenia, antipsychotics, QT prolongation.

INTRODUCTION

Schizophrenia has a prevalence of ~1.1% in the United States, with nearly 2.2 million US adults diagnosed with the condition (W.E. Narrow, unpublished data, 1998).[1] Antipsychotic medications are the first line of therapy for this disorder and have been shown to effectively control its various symptoms. However, these agents also are associated with a number of side effects, ranging from extrapyramidal symptoms to cardiac disorders.[2]

An important concern with antipsychotics used for the treatment of schizophrenia is the prolongation of the QT interval on electrocardiography. In some instances, QT prolongation can lead to a polymorphic ventricular tachycardia known as torsades de pointes.[3] QT prolongation may be caused to varying degrees by different antipsychotics. Of the typical antipsychotics, haloperidol, droperidol, chlorpromazine, mesoridazine, pimozide, and thioridazine have all been reported to cause QT prolongation. Thioridazine has been most consistently shown to carry the risk of QT prolongation and subsequent torsades de pointes. Of the atypical antipsychotics, quetiapine, risperidone, and ziprasidone have been shown to cause QT prolongation.[3–5]

This issue of antipsychotic-induced arrhythmia has assumed paramount importance, especially in light of a high incidence of cardiovascular mortality and morbidity in patients with schizophrenia, with 1 study[6] estimating the incidence to be nearly 1.5-fold higher in these patients compared with controls. An important reason for this elevated cardiac risk may be frequent overdose of medications and high prevalence of comorbid substance abuse disorder, with studies[3,7] estimating nearly 50% of schizophrenic patients to be experiencing comorbid substance abuse disorders. Drugs used to treat other conditions also may cause QT prolongation. Some of these conditions, such as depression,

commonly occur in patients with schizophrenia,[8] representing an additional risk factor for higher prevalence of cardiovascular complications in schizophrenic patients compared with the general population.[9,10]

Warner et al[11] demonstrated higher rates of QT abnormalities in patients with schizophrenia than in controls and a distinct association with the use of antipsychotics ($P < 0.05$). Reilly et al[12] found increasing age ($P = 0.04$) and use of typical antipsychotics such as thioridazine ($P = 0.001$) and droperidol ($P = 0.004$) to be risk factors for QT prolongation. It has been shown that ~25% of patients using antipsychotics demonstrate abnormal QT-interval prolongation, which can increase the risk of serious ventricular arrhythmias.[12,13]

Although there is no direct evidence linking QT prolongation with the risk of torsades de pointes, QT prolongation has been consistently identified as an important predictor of sudden death in patients with schizophrenia.[14] The published literature includes numerous case reports of torsades de pointes and sudden death in patients taking thioridazine, haloperidol, risperidone, and other antipsychotics.[13,15–17] After examining all 24,158 medicolegal autopsies in Finland over a 3-year period, Mehtonen et al[18] found 49 (0.2%) sudden unexpected deaths among apparently healthy adults taking psychotropic medications. Cohort studies of schizophrenic patients have reported a consistent disproportion of cardiovascular disease mortality, which may be at least partly attributed to the use of antipsychotic drugs.[6,19,20] One of the most recent studies of this topic, conducted by Ray et al[10] using Tennessee Medicaid data, revealed that the risk of sudden cardiac death for those using antipsychotic drugs was 2.39 times greater than that for nonusers after controlling for age, sex, presence of cardiovascular disease, major depressive disorder, and smoking status.

Previous studies have demonstrated that the clinical significance of a QT-prolonging effect of a drug can be greater for individuals with preexisting QT-prolonging conditions or from concomitant use of QT-prolonging medications.[21,22] A majority of the available data consists of case reports of torsades de pointes or deaths that are presumed to have resulted from an additive effect due to concurrent use of QT-prolonging drugs. Therefore, clinicians have recommended that concomitant QT-prolonging medications should be avoided or prescribed with caution for schizophrenic patients.[23]

Clinical trials for newer antipsychotic medications have demonstrated less impact on the QT interval.[24] However, patients who are more susceptible to QT prolongation (eg, elderly and female patients) are generally underrepresented in such trials.[25,26] In addition, patients with preexisting cardiovascular problems and those using other QT-prolonging drugs (ie, those with other important risk factors) are generally excluded from such trials.[24] Thus, the safety profile of these new antipsychotics cannot be extrapolated to the general patient population. An example of this is the approval of the atypical antipsychotic sertindole for use in the European market in 1996. After the clinical trials, it was approved

to be prescribed for patients with schizophrenia. However, in 1998, the Committee on Safety of Medicines in the United Kingdom found evidence of 36 unexplained deaths and 13 serious but nonfatal arrhythmias. As a result, the drug was initially suspended and then removed from the European market.[27–29]

The objective of this study was to assess the utilization of QT-prolonging drugs and the prevalence of medical conditions causing QT prolongation in a large population of patients with schizophrenia in real-world practice settings. Medicaid claims provide an appropriate database to examine this issue because high proportions of patients with schizophrenia are enrolled in Medicaid; loss of employment due to disabilities and psychotic symptoms is not uncommon in patients with schizophrenia, resulting in the government's paying for >60% of expenditures for schizophrenia treatment.[30] We hypothesized that the results of this study would demonstrate the prevalence of schizophrenic patients at higher risk for complications related to QT prolongation. We hoped that this study also would assist in the formulation of clinical practice guidelines in the treatment of schizophrenia.

PATIENTS AND METHODS

Data Source

This retrospective study was conducted using medical and pharmacy claims from enrollees in West Virginia's Medicaid program. The data consisted of 3 types of files: provider files, recipient files, and claims (medical and pharmacy) files. The provider files contained specific information about all health care providers eligible to deliver services to Medicaid recipients. The recipient files contained detailed information about Medicaid recipients, such as name, Medicaid number, eligibility information, aid category, sex, race, and mailing address. The claims files stored detailed information specific to processed claims. For each medical claim, the file contained the following information: invoice type; provider number; recipient number; *International Classification of Diseases, Ninth Revision, Clinical Modification* (*ICD-9-CM*),[31] code of diagnosis for which the service was provided; common procedural terminology code for procedures and services provided; diagnostic-related group codes; date claim was submitted; date of adjudication; through-date of service; coordination of benefit code; and total amount paid. For each pharmacy claim, the file included the following information: number of days' supply; metric quantity; date dispensed; National Drug Classification (NDC) code; generic code; therapeutic class code; refill number; provider identification number; and amount paid.

Study Population

Patient identifiers were encrypted for this study to protect patient confidentiality. The study was approved by the institutional review board at West Virginia University (Morgantown, West Virginia). Because Medicaid recipients aged ≥65 years are eligible for coverage under both Medicaid and Medicare, this research

was restricted to Medicaid recipients aged 18 to 64 years. For similar reasons, Medicaid recipients who were part of other managed care programs were excluded.

Data Analysis

Patients were identified on the basis of *ICD-9-CM* codes for schizophrenia (ie, 295.XX). Patients with ≥1 medical claim for schizophrenia between January 1, 1997, and December 31, 1999, were included in the study. Within this time period, the date of the first claim with a diagnosis of schizophrenia was treated as an index date. Medical and pharmacy claims for these patients were then examined for a 1-year period after the index date. To prevent underestimation of drug utilization and prevalence of medical conditions, only recipients who were continuously eligible during the analysis period were included in the study.

A comprehensive list of QT-prolonging drugs was obtained from the published literature search (Appendix I).[4,32,33] The QT-prolongation potential of each drug was based on either US Food and Drug Administration–approved drug labeling or case reports of QT prolongation/torsades de pointes. These drugs were identified in the prescription claims data using their specific NDC codes.

Drug utilization was assessed in terms of the number of QT-prolonging drugs and the total number of prescriptions filled for all QT-prolonging drugs. For example, if an enrollee had 3 prescription claims for the QT-prolonging drug erythromycin and 2 prescription claims for fluoxetine in the study period, then for that enrollee, the number of QT-prolonging drugs was 2 and the total number of prescriptions filled for all QT-prolonging drugs was 5.

Statistical Analysis

Descriptive statistics were used to ascertain the utilization of these drugs. The proportion of patients using ≥1 QT-prolonging drug in the study period was computed. For these patients, the mean numbers of QT-prolonging drugs used and prescriptions filled per year were reported. However, because antipsychotics are the mainstay of drug therapy for patients with schizophrenia and because several antipsychotics may prolong the QT interval (see Appendix I), these numbers may have been inflated. Therefore, a subanalysis excluding all QT-prolonging antipsychotics was performed. In addition, because the claims data did not provide prescription information for inpatients, these analyses were also conducted after adjusting for number of inpatient days during the study period.

A comprehensive list of medical conditions causing QT prolongation was obtained from the published literature search (Appendix II).[32] *ICD-9-CM* codes from the medical claims file were used to identify these conditions and ascertain their prevalence in our study sample. The proportion of patients having ≥1 condition causing QT prolongation was computed. For these patients, descriptive statistics (eg, mean number of medical conditions per year) were also reported.

Patients were also categorized based on their utilization of QT-prolonging drugs and the presence of medical conditions causing QT prolongation. The proportion of patients in each of these categories was computed. Also, differences in drug utilization and prevalence of medical conditions leading to QT prolongation between patients with different demographic characteristics, such as age and sex, were examined using multiple analysis of variance (MANOVA). Subsequent analysis of variance (ANOVA) and a post hoc Scheffé test were used to determine specific differences. An a priori α level of 0.05 was used for all analyses. Thus, $P \leq 0.05$ was considered significant. All statistical analyses and data manipulations were performed using the Statistical Package for Social Sciences version 10.0 (SPSS Inc., Chicago, Illinois).

RESULTS

On the basis of the inclusion criteria, 1946 patients with schizophrenia were identified from the claims data. Twenty-two patients were then excluded because of insufficient or missing demographic data. Of the remaining 1924 patients, 1699 were continuously eligible for a 1-year period after the index date, thus forming the study sample.

The mean (SD) age of this final sample was 40.8 (11.35) years (range, 18–63 years); 54.7% of the patients were women. The mean (SD) number of inpatient days was 8.8 (18.4) (range, 0–275 days). A total of 90.8% of the patients received ≥1 prescription for an antipsychotic agent during the study period. Those prescribed an antipsychotic received a mean (SD) of 17.53 (16.50) prescriptions for antipsychotic agents during the 1-year study period. Seventy-four percent of these antipsychotic prescriptions filled were for atypical antipsychotics.

Examining the utilization of all QT-prolonging drugs showed that 87.1% of the patients used ≥1 QT-prolonging drug during 1 year, with a mean (SD) of 2.6 (1.6). Among patients using such agents, a mean (SD) of 15.4 (10.3) prescriptions were filled during the study period.

Analyses restricted to nonantipsychotic QT-prolonging drugs demonstrated that 76.9% of patients received ≥1 nonantipsychotic QT-prolonging drug in a year, with a mean (SD) of 2.1 (1.3) such drugs used per patient per year. Patients using ≥1 nonantipsychotic QT-prolonging drug filled a mean (SD) of 11.4 (8.2) prescriptions per year. These numbers were also computed adjusting for absence of prescription data for inpatients. However, the results were not found to be significantly different.

Among the nonantipsychotic QT-prolonging drugs used by patients with schizophrenia, 86.6% were prescribed for psychiatric purposes. Among these, lithium was the most commonly used, prescribed to 17.1% of all schizophrenic patients in the study. Antibacterial agents constituted the majority of QT-prolonging drugs that were used for nonpsychiatric purposes. A detailed list

of the most frequently used psychiatric and nonpsychiatric QT-prolonging drugs is provided in Table I.

Analysis of medical claims data using *ICD-9-CM* codes revealed that 15.9% of patients with schizophrenia had ≥1 medical condition associated with QT prolongation. Patients with ≥1 such condition had a mean (SD) of 1.2 (0.57) conditions potentially causing QT prolongation. Hypothyroidism was the most prevalent medical condition causing QT prolongation, followed by myocardial infarction.

The figure provides a detailed categorization of patients based on their utilization of QT-prolonging drugs and the presence of medical conditions causing QT prolongation. Results of the MANOVA revealed that utilization of nonantipsychotic QT-prolonging drugs, prescriptions filled, and prevalence of medical conditions leading to QT prolongation significantly differed on the basis of age (Wilks $\lambda = 0.96$, $P < 0.001$) and sex (Wilks $\lambda = 0.97$, $P < 0.001$). Univariate ANOVA revealed that the number of nonantipsychotic QT-prolonging drugs used was significantly higher among women than men ($P < 0.001$). However, no significant differences were observed between age categories. On the other hand, significant differences were observed in terms of both age (both $P < 0.001$) and sex (both $P < 0.001$) for number of prescriptions filled and number of medical conditions (both $P < 0.001$). A detailed breakdown for the univariate analyses is provided in Table II.

A post hoc Scheffé test revealed significantly more prescriptions filled per year for patients aged 34 to 49 years ($P < 0.01$) and 50 to 64 years ($P < 0.001$) compared with those aged 18 to 33 years. Also, patients in the older age category (50–64 years) had significantly more medical conditions causing QT prolongation than patients aged 18 to 33 years ($P < 0.001$) or 34 to 49 years ($P < 0.001$).

DISCUSSION

The list of QT-prolonging drugs includes several used for psychiatric purposes, such as antipsychotics and antidepressants. Because antipsychotics are the

Table I. Most frequently used nonantipsychotic QT-prolonging drugs in patients with schizophrenia (n = 1699).

Psychiatric Drugs		Nonpsychiatric Drugs	
Drug	Percent	Drug	Percent
Lithium	17.1	Trimethoprim/sulfamethoxazole	15.7
Fluoxetine	14.7	Clarithromycin	10.0
Sertraline	14.0	Erythromycin	6.1
Paroxetine	13.5	Levofloxacin	6.1
Fluphenazine	11.8	Diphenhydramine	6.0

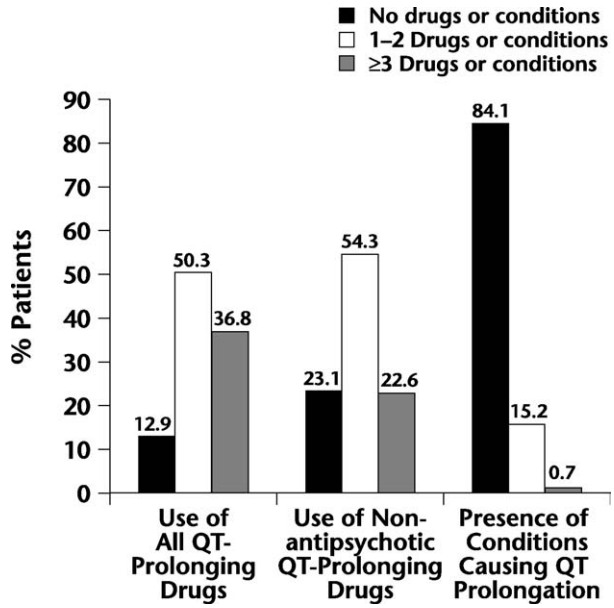

Figure. Proportion of schizophrenic patients using QT-prolonging drugs and having medical conditions leading to QT prolongation (n = 1699).

mainstay of therapy for schizophrenia and because there is a high prevalence of depression in schizophrenic patients, concomitant use of QT-prolonging drugs is likely in such a population. The results of the present study suggested the same, showing that ~87% of the enrolled patients had used ≥1 QT-prolonging drug in a year, with a mean (SD) of 15.4 (10.3) prescriptions filled for these drugs.

As previously mentioned, concomitant use of QT-prolonging drugs can be a major risk factor for cardiac events such as torsades de pointes. We found the use of QT-prolonging drugs to be significantly higher in women and older patients, raising concern about prescribing patterns in schizophrenic patients. It is notable that the atypical antipsychotics vary in their potential to cause prolongation of the QT interval. In the clinical setting, care should be taken to prescribe antipsychotics not associated with QT prolongation in patients who already use QT-prolonging drugs for other conditions and in patients whose conditions create a predisposition to QT prolongation. High utilization of QT-prolonging drugs and an increased prevalence of medical conditions causing QT prolongation should make the QT-prolonging profile of an antipsychotic an important factor in both prescribing patterns and inclusion of antipsychotics in drug formularies.

Table II. Differences in utilization of drugs and prevalence of conditions leading to QT prolongation on the basis of sex and age (n = 1699).

	Mean (SD) No. of Nonantipsychotic QT-Prolonging Drugs per Year	Mean (SD) No. of Nonantipsychotic QT-Prolonging Prescriptions Filled per Year	Mean (SD) No. of Medical Conditions Leading to QT Prolongation
Sex			
Women	1.8 (1.5)	9.6 (8.8)	0.3 (0.6)
Men	1.4 (1.3)	7.8 (8.5)	0.1 (0.4)
F test score	38.90	18.50	25.50
P	<0.001	<0.001	<0.001
Age group, y			
18–33	1.6 (1.5)	7.5 (8.3)	0.1 (0.4)
34–49	1.6 (1.4)	9.0 (8.6)	0.2 (0.4)
50–64	1.6 (1.3)	9.7 (9.0)	0.3 (0.7)
F test score	0.00	7.60	19.40
P	NS	<0.001	<0.001

This study is subject to several limitations, some of which are inherent in investigations that rely on the use of health claims data, such as errors due to billing and coding. The study results are limited to enrollees aged 18 to 64 years who were not part of managed care in the West Virginia Medicaid program. Therefore, they may not be generalizable to other state Medicaid programs or populations because the West Virginia Medicaid population may not be representative of other states in terms of age, sex, and other sociodemographic characteristics. Only drugs reimbursed by West Virginia Medicaid were examined. Drug utilization information about over-the-counter drugs and prescription samples received in the physician's office were not measurable. This may have led to an underestimation of overall drug utilization.

In this study, we identified drugs associated with QT prolongation by combining lists from 3 literature sources. We followed this procedure in an effort to be thorough; however, doing so may have introduced a degree of error to our results. We did not critically assess the criteria by which drugs were added to the QT-prolonging list from each of the sources, and there may have been instances in which drugs were added to these lists with little or no objective evidence. This would have tended to inflate our results.

It should also be noted that the lists of QT-prolonging drugs identified in the literature were categoric (thus, if there was any evidence of this adverse event, the drug was added to the list). In truth, the frequency of occurrence of QT prolongation is likely to be both variable and dependent on the properties of the individual drug and individual patient characteristics. If a drug is not

likely to cause QT prolongation, the medical benefit of the drug may be worth the potential risk. Therefore, the overall clinical significance of our findings may be somewhat muted when considering the nature of the decisions that must be made in clinical practice.

Also, there is a possibility of initial misdiagnosis with mental disorders such as schizophrenia. As a result, identification of patients from administrative claims data on the basis of single *ICD-9-CM* diagnostic codes may potentially cause misclassification bias. However, in our study, we examined prevalent cases (ie, those with preexisting schizophrenia), in which the issue of initial misdiagnosis was not a major concern. In addition, a study by Lurie et al[34] showed that most schizophrenia diagnoses in Medicaid claims were accurate, justifying the use of single *ICD-9-CM* diagnostic codes for patient identification. Also, some patients who had problems with QT prolongation in the past may have subsequently stopped using QT-prolonging medications. Thus, the sample may have failed to capture many patients who discontinued therapy due to QT prolongation. This phenomenon could have led to underestimation of the utilization of such drugs in the population studied.

Occurrence of clinical events related to drug utilization and presence of medical conditions were not measured. Thus, this study failed to provide a correlation between the use of QT-prolonging drugs and clinical events such as QT prolongation and subsequent torsades de pointes. This important research issue should be examined in future studies. Our study provides an insight into the potential use of administrative claims data for the purpose of addressing such research questions.

CONCLUSIONS

In this study, a high utilization of QT-prolonging drugs and an increased prevalence of medical conditions causing QT prolongation were found. Therefore, prescribing antipsychotic drugs for patients with schizophrenia should entail assessment of predisposing risk factors, such as concurrent use of other QT-prolonging drugs and the presence of cardiovascular and other conditions associated with QT prolongation, especially in women and older patients with schizophrenia.

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Appendix I. Drugs that prolong the QT interval and/or induce torsades de pointes.[4,32,33]

Amantadine	Felbamate	Lithium	Risperidone*
Amiodarone	Flecainide	Maprotiline	Salmeterol
Amitriptyline	Fluoxetine	Mesoridazine*	Sertraline
Bepridil	Fluphenazine	Moexipril/HCT2	Sotalol
Bretylium	Foscarnet	Moxifloxacin	Sparfloxacin
Chloral hydrate	Fosphenytoin	Naratriptan	Sumatriptan
Chloroquine	Gatifloxacin	Nicardipine	Tacrolimus
Chlorpromazine*	Grepafloxacin	Octreotide	Tamoxifen
Cisapride	Halofantrine	Paroxetine	Thioridazine*
Citalopram	Haloperidol*	Pentamidine	Tizanidine
Clarithromycin	Hydroxyzine	Pimozide*	Trifluoperazine hydrochloride*
Desipramine	Ibutilide	Probucol	Trimethoprim-sulfamethoxazole
Diphenhydramine	Imipramine	Procainamide	Vasopressin
Disopyramide	Indapamide	Prochlorperazine*	Venlafaxine
Dofetilide	Isradipine	Propafenone	Ziprasidone*
Doxepin	Ketoconazole	Quetiapine*	Zolmitriptan
Droperidol*	Levofloxacin	Quinidine	
Erythromycin	Levomethadyl	Quinine	

*QT-prolonging antipsychotic.

Appendix II. Medical conditions that may cause prolongation of QT interval.[32]

Cerebrovascular accident	Hypothyroidism
Complete atrioventricular block	Myocardial ischemia or infarction
Encephalitis	Myocarditis
Hyperaldosteronism	Rheumatic fever
Hyperparathyroidism	Romano-Ward syndrome
Hypocalcemia	Severe bradycardia
Hypokalemia	Sinus node dysfunction
Hypomagnesemia	Subarachnoid hemorrhage